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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/646,063 | 08/22/2003 | Martin H. Teicher | 04843/113003 | 8435 |

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| EXAMINER | |
|---|---|
| CORDERO GARCIA, MARCELA M | |
| ART UNIT | PAPER NUMBER |
| 1654 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/22/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/646,063 | TEICHER ET AL. | |
| | Examiner | Art Unit | |
| | Marcela M. Cordero Garcia | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-11, 16-18, 24 and 26-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15,19-23,25 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

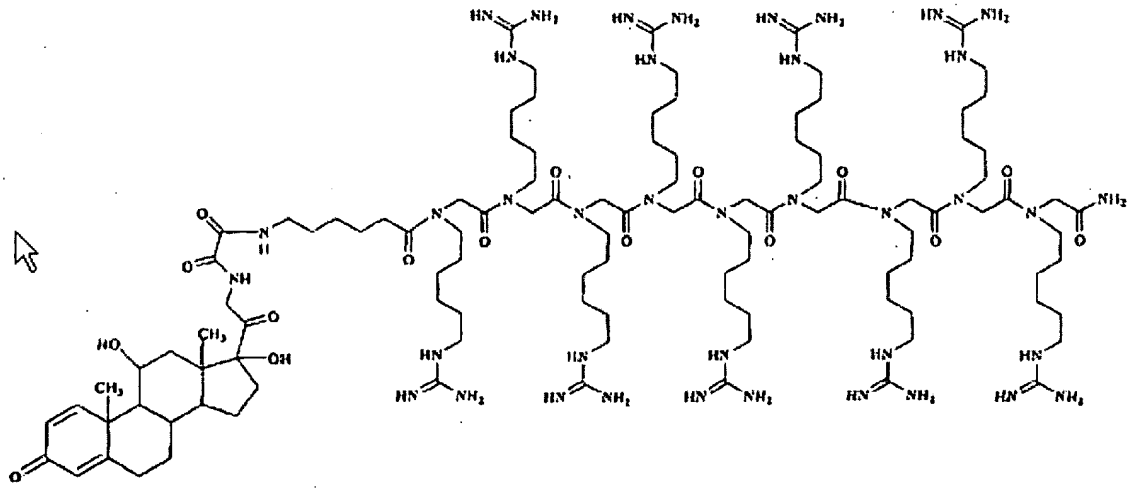
## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 4, 2007 has been entered.

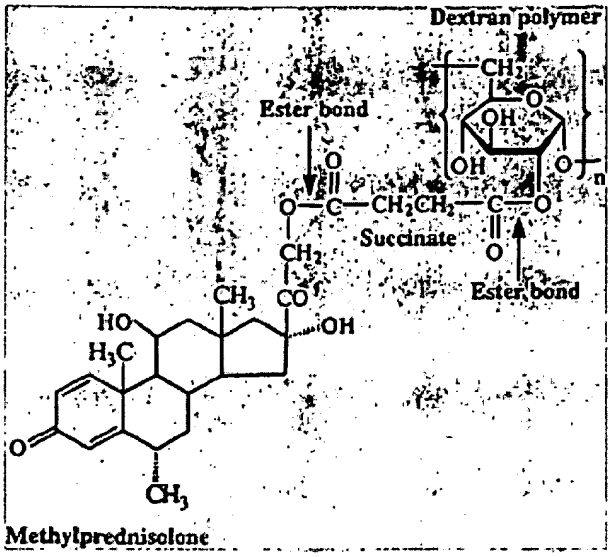
Claims 1-32 are pending in the application. Claim 12 has been amended.

Applicant elected Group II, drawn to claims 12-15 and 19-32. Applicant also elected the following species: a method of rheumatoid arthritis with



C

The species (drawn to claims 12, 13, 15, 19-23, 25, 28-32) above was searched and found free of the prior art, however please note the outstanding 35 USC 112 rejections below. Examiner broadened the search and found the following species: a method of treating rheumatoid arthritis and/or organ/tissue transplant rejection with




Claims 12-15, 19-23. 25, 28-32 are presented for examination on the merits as they read upon the instant species. Claims 1-11, 16-18 and 24, 26-27 are withdrawn as not drawn to the elected group or to either species.

***New grounds of rejection***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-15 and 19-23, 25 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that

the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to

distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

***In the instant case, the claims are drawn to a method of treating an autoimmune or inflammatory condition in a mammal comprising administration of a corticosteroid attached to a group that is either a bulky group of greater than 400 Daltons or charged group of less than 400 Daltons in an amount effective to treat said condition, wherein said corticosteroid conjugate (i) has anti-inflammatory activity in vivo, (ii) has reduced activity in the central nervous system in comparison to said corticosteroid without said group and (iii) is resistant to in vivo cleavage, such that in vivo less than 10% of the administered***

***corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion.*** In regards to the "bulky group of greater than 400 Daltons" term, this is a very broad generic statement drawn to any chemical structure with a extremely broad molecular weight range (>400 Da), there exists a plethora of such compounds, which are not adequately described and/or represented in the examples (page 19, lines 4-22 and page 20). By the same token, the terms "charged group of less than 400 Daltons is very broad, encompassing any charged chemical composition and structure including charged polypeptides, charged polysaccharides and so forth (see, e.g., page 21, lines 1-12). In addition, the term "corticosteroid" encompasses any corticosteroids with any chemical structure including structurally/biologically similar compounds (e.g., disclosure, page 11, lines 1-29, pages 12-14). The claims are drawn, to methods of using corticosteroid conjugates (including dimers, trimers and so forth) with the bulky or charged groups to treat autoimmune and inflammatory conditions such as asthma, psoriasis, eczema, organ/tissue transplant rejection, graft vs. host reactions, Raynaud's syndrome, autoimmune thyroiditis, Grave's disease, autoimmune hemolytic anemia, autoimmune throboeytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease, Sjogren's syndrome, urticaria, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, Chron's disease, ulcerative colitis, lupus, tendonitis, bursitis, adult respiratory distress syndrome, shock, oxygen toxicity, glomerulonephritis, vasculitis, reactive arthritis, necrotizing enterocolitis, Goodpasture's syndrome, hypersensitivity pneumonitis, glomerulonephritis, encephalomyelitis and meningitis. A mere statement that such compounds would be desirable for treatment of a host of diseases does not sufficiently provide ample written description pages describing the full breadth of the corticosteroids-bulky group and corticosteroids-charged group conjugates and

specifically of the biological activity required to treat a host of diseases as instantly claimed. The specification does provide examples of what qualify as compounds of the claimed invention (see, e.g, disclosure, pages 29-36, Examples 3-8), however, these are limited to a few examples such as a polyguanidine peptoid derivative of prednisolone (Example 3), a hyaluronic acid conjugate of triamcinolone (Example 5), an mPEG conjugate of Budesonide (Example 6), a beclomethasone dimer (Example 7). As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of polymer with any biomolecule. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide examples of methods of treating administrating conjugates of a representative number of corticosteroid conjugates encompassed by the instant claims or of any of the instantly claimed diseases description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does

"little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claims 12-15 and 19-23, 25 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The disclosure defines the term "treating" refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes (e.g., page 9, lines 3-10). The instant "treating" methods therefore encompass using the claimed compounds to prevent autoimmune or inflammatory conditions such as asthma, psoriasis, eczema, organ/tissue transplant rejection, graft vs. host reactions, Raynaud's syndrome, autoimmune thyroiditis, Grave's disease, autoimmune hemolytic anemia, autoimmune throboeytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease, Sjogren's syndrome, urticaria, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, Chron's disease, ulcerative colitis, lupus, tendonitis, bursitis, adult respiratory distress syndrome, shock, oxygen toxicity, glomerulonephritis, vasculitis, reactive arthritis, necrotizing enterocolitis, Goodpasture's syndrome, hypersensitivity pneumonitis, glomerulonephritis, encephalomyelitis and meningitis, which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" is an absolute definition, which means to stop from occurring and, thus,

requires a higher standard for enablement than does "therapeutic", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders as asthma, psoriasis, eczema, organ/tissue transplant rejection, graft vs. host reactions, Raynaud's syndrome, autoimmune thyroiditis, Grave's disease, autoimmune hemolytic anemia, autoimmune throboeytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease, Sjogren's syndrome, urticaria, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, Chron's disease, ulcerative colitis, lupus, tendonitis, bursitis, adult respiratory distress syndrome, shock, oxygen toxicity, glomerulonephritis, vasculitis, reactive arthritis, necrotizing enterocolitis, Goodpasture's syndrome, hypersensitivity pneumonitis, glomerulonephritis, encephalomyelitis and meningitis (which clearly are not recognized in the medical art as being totally preventable conditions).

***Rejections Maintained***

***Claim Rejections - 35 USC § 102***

Claims 12-15, 19-23 and 28-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (J Pharm Sci, 2001).

Zhang et al. teach a method of treating rheumatoid arthritis and/or organ transplantation condition in a mammal, said method comprising administering to said mammal (page 2080, column 1, lines 1-20) a corticosteroid conjugate comprising a

corticosteroid (6α-methylprednisolone, page 2079, column 2, lines 9-16, Scheme 1) attached to a group that is a bulky group of greater than 400 daltons (Dextran-70, 70,000 Da page 2079, column 2, lines 9-12, Scheme 1) in an amount effective to treat said condition, wherein said corticosteroid conjugate (i) has anti-inflammatory activity *in vivo*, (ii) reduced activity in the central nervous system in comparison to said corticosteroid without said group and (iii) is resistant to *in vivo* cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion. (see entire document, e.g., abstract and column 1, paragraph 1, page 2079, Scheme I, page 2079 and pages 2085-2086). The limitation of claim 15 is taught, e.g., at page 2080, column 1, lines 8-10. The limitations of claim 20 are taught at Scheme 1, page 2079, wherein the corticosteroid methylpredisolone has the structure of formula I with the bond between $C_1$ and $C_2$ is a double bond, $X_1$ represents H, $X_2$ represents $CH_3$, $X_3$ represents H, $R_1$ represents OH, $R_2$ represents $CH_2OH$ (before conjugation), $R_3$ represents OH and $R_4$ represents H. The limitations of claim 21 are taught at Scheme 1, page 2079, wherein the linker is described by formula III wherein $G^1$ is a bond between said corticosteroid and said linker, $Z^1$ is O, o is 1, $Y^1$ is carbonyl, u is 1, s is zero, $R^{10}$ is $C_2$ alkyl, t is zero, $Y^2$ is carbonyl, v is 1, $Z^4$ is O, p is 1, $G^2$ is a bond between said linker and said bulky group. Bulky groups encompass charged groups as taught in the disclosure at page 19, lines 18-22. Please note that (1) the administered subject has not been defined and (2) the term "treating" has been defined as encompassing prevention of the disease(s) and therefore, either case (1) or (2) allows for the claims to read upon a method wherein the

subject is not affected with any of the claimed disease (s). Therefore, the reference is deemed to anticipate the instant claims above.

Applicant argues that the amended claims have now been amended to clarify in limitation (iii) that resistance to *in vivo* cleavage refers not to the rate at which cleavage occurs *in vivo*, but rather the extent to which cleavage occurs prior to excretion and provides a 1.132 declaration by Teicher that estimates (based on a reference by Mehvar et al.) that 50% of the conjugate would be cleaved prior to clearance.

Applicant's arguments have been carefully considered by Examiner, but not deemed persuasive because, the limitations (i), (ii) and (iii) appear after a wherein clause, and according to MPEP 2111.04 [R-3], "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;
(B) "wherein" clauses; and
(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In Hoffer v. Microsoft Corp., 405 F. 3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention. " *Id.* However, the court noted (quoting Minton v. Nat 'l Ass 'n of Securities Dealers, Inc., 336 F. 3d 1373, 1381, 67 USPQ2d 1614, 1620

(Fed. Cir. 2003)) that a "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" *Id.* In the instant case, the method taught by Zhang teaches conjugates reciting all structural elements of those used within the method instantly claimed, therefore, any functional effects of the conjugates such as (i), (ii) and (iii) are deemed inherent to such molecular structure.

***Conclusion***

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
Art Unit 1654

MMCG 03/07

ANISH GUPTA
PRIMARY EXAMINER